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Original Article

Exploring Memory Systems After Pediatric Posterior Fossa Tumor: From Memory Profile Comparisons in Nonirradiated Versus Irradiated Patients to Episodic Memory Tests Capable of Detecting Radiation-induced Hippocampal Damage

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Abstract

Aims: Pediatric posterior fossa tumor (PFT) survivors experience long-term cognitive sequelae, including memory disorders, for which irradiation is one of the main risk factors. The aims of the present study were to (1) explore the profile of impairment in episodic, semantic, working and procedural memory systems in irradiated versus nonirradiated PFT survivors, and (2) test whether an autobiographical questionnaire and a two-phase ecological test (Epireal) assessing episodic memory are more sensitive to radiation-induced hippocampal damage than commonly used tests.

Materials and methods: A total of 60 participants (22 irradiated PFT survivors, 17 nonirradiated PFT survivors, and 21 controls) were included in the prospective IMPALA study. They all underwent a broad battery of tests assessing the different memory systems in two 2-day sessions 3 weeks apart. We performed between-groups comparisons and analyzed impairment profiles, using -1.65 *SD*s as a cut-off. For irradiated patients, correlations were calculated between mean radiation doses to key brain structures involved in memory (hippocampus, cerebellum, and striatum) and corresponding memory scores.

Results: PBT survivors performed significantly more poorly than controls ($p < 0.001$) on conventional tests of episodic, semantic and working memory: 64% of irradiated patients and 35% of nonirradiated patients had a deficit in at least two memory systems, with episodic memory impairment being more specific to the irradiated group. Epireal had a larger effect size than the other episodic memory tests, allowing us to detect deficits in a further 18% of irradiated patients. These deficits were correlated with the mean radiation dose to the left hippocampus.

Conclusion: Memory impairment is a frequent long-term cognitive sequela in PFT survivors, especially after radiation therapy. New ecological tests of episodic memory that are more sensitive to radiation-induced deficits than conventional tests could yield specific markers of the toxicity of medial temporal lobe irradiation.

Key words: Children; Episodic memory; Hippocampus; Posterior fossa brain tumor; Radiotherapy

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Introduction

Brain tumors are the main type of solid tumors in children. Two-thirds of them are located in the posterior fossa, and these mainly take the form of medulloblastomas (40%), pilocytic astrocytomas (30%), and ependymomas (10%). Mean 5-year survival is around 70–80%, depending on the nature of tumor, ranging from 40% for ependymoma to 90% for medulloblastoma and 99% for pilocytic astrocytomas [1]. In the past couple of decades, the management of sequelae, particularly cognitive ones, has become an increasingly important issue after a pediatric brain tumor. Irradiated patients are particularly liable to develop long-term impairments in attention, processing speed, and memory [2]. These sequelae can lead to poor academic achievement and difficulty finding a job [3].

It is important to identify the profile of memory impairment in patients with pediatric posterior fossa tumor (PFT), in order to guide clinical follow-up and cognitive rehabilitation. Until now, studies exploring memory among PFT survivors have tended to focus on long-term declarative (episodic and semantic memory) and short-term working memory performances, missing the nondeclarative part of memory (procedural memory) and the interactions between these systems [4].

Patients' irradiation status appears to be the main risk factor for memory impairment. More specifically, hippocampal irradiation had been linked to poorer performances on conventional episodic memory tests [5–7]. The challenge of defining radiotherapy (RT) dose constraints for this structure remains unresolved, questioning the relevance of the neuropsychological tests that are currently used to explore hippocampal function. Up to now, researchers have mainly used face recognition and word list learning and their immediate or delayed recall at 20–30 minutes. Although these tests are validated and standardized markers of long-term anterograde memory, they offer an incomplete assessment of episodic memory as defined by Tulving in 1972. Episodic memory allows us to remember personally experienced events, together with their spatio-temporal context of acquisition and sufficient phenomenological details to mentally project ourselves back to these past events and consciously *relive* them. A range of tests have been developed to take these components into account. With autobiographical questionnaires, participants have to remember a personal event, but this means that the encoding of their memories is not controlled. With more ecological tests, events are encoded during an initial neuropsychological assessment and recalled a few days later. So far, one study has assessed episodic memory in child survivors using an autobiographical questionnaire [8], and one using an ecological task where participants were told a story involving different smells and then had to recall it [9]. Both reported poorer performances in irradiated patients.

In the present study, we explored the different memory systems in irradiated versus nonirradiated pediatric PFT survivors. We aimed to answer the following three questions regarding this population: (1) Do irradiated and nonirradiated survivors have different memory profiles? (2) Are the neuropsychological tests that are currently used the most suitable ones for assessing episodic memory outcome in survivors? (3) Are autobiographical questionnaires and ecological tests more sensitive to radiation-induced brain damage? We hypothesized that working memory and procedural memory deficits are common to all PFT survivors, and are related to damage to cerebellocortical networks, whereas declarative memory deficits (including episodic and semantic memory systems) are specific sequelae of complementary treatments and, especially, are dependent on the radiation dose to the hippocampus. We also hypothesized that assessing episodic memory with more specific tests can provide a better understanding of the difficulties encountered by patients, and more accurate markers of hippocampal damage.

Methods

Participants

A total of 60 participants were included in this prospective study between January 2020 and September 2021. Patients were recruited from Cancer Institute and Children's Hospital and healthy volunteers were recruited via a call for volunteers in the press [10]. We compared 22 PFT survivors whose treatment had included focal or craniospinal irradiation (irradiated group) with 17 PFT survivors who had not been treated with radiotherapy (nonirradiated group) and 21 participants (control group) with no neurological or psychiatric history, matched on sex, age and handedness with the irradiated group. An institutional review board approved the study protocol. Written informed consent was obtained either from participants or from their parents, if they were aged below 18 years.

Neurocognitive Assessment

Memory Assessment

Episodic Memory. Episodic memory was assessed with the following tests:

- Visual anterograde long-term memory: the Faces subtest of the Children's Memory Scale (CMS; [11]) for children $<$16 years or the Wechsler Memory Scale–3rd edition (WMS-III) for children $\geq$16 years [12]. In this validated and standardized subtest, participants are shown 24 target faces, one at a time for 2 seconds. They are then shown 48 faces (24 targets and 24 distractors) and have to identify the target faces by responding either "yes" or "no" to each face (immediate recognition score). Participants are encouraged to memorize the target faces. After a 30-minute interval, participants are shown the same 48 faces (24 targets and 24 distractors) and again have to identify the target faces (delayed recognition score)

- Verbal anterograde long-term memory: the Word List subtest of the CMS for children <16 years or the WMS-III for children ≥16 years. In this validated and standardized subtest, a list of 12 words is read out to participants, who have to recall the list of words in four trials (learning score). After a 30-minute interval, participants are asked to recall the list of words (delayed recall score), and nonrecalled words are cued (cued recall score)
- Autobiographical questionnaire [13]: Participants are asked to recall as many details as possible about the previous evening's meal and about a previous holiday (free recall score). The expected elements that are not recalled are cued (cued recall score). Ten expected elements are scored, with 2 points for freely recalled elements, and 1 point for cued recall. Each memory (i.e., dinner and holiday) is scored out of 20 points. The accuracy of the memories was not checked with a parent to ensure the authenticity of the statements
- Epireal adapted for children: Eight mini-events occurred in a standardized way during the neuropsychological assessment. These involved the participant as either an actor or a spectator. For example, in one of the mini-events in which the participant was an actor, the neuropsychologist asked the participant to pass a blue binder that was in a predefined position on the examiner's desk to the participant's right. Three weeks later, participants were asked to recall the neuropsychological assessment with as many details as possible (free recall score). Nonrecalled elements were cued (cued recall score), and if they were still not recalled, the participant was asked a multiple-choice question (recognition score). Three scores of episodicity were calculated, reflecting the quality and detail of memories for the object (*what*), the spatial context (*where*), and the temporal context (*when*). In a population of adult patients with temporal epilepsy, this test was found to be more specific to participants' real-life memory performances than the usual memory tests [14]. Minor changes were made to this test to adapt it to a child population.

The study started in February 2020. Owing to the first COVID-19 lockdown, the interval between the two sessions exceeded 30 days for two participants in the irradiated group, and two in the nonirradiated group. Excluding these participants from the analyses did not change the between-group results. To avoid further issues, for the rest of the study, if the interval risked being too long for participants, instead of waiting for the second session, we tested their recall of the Epireal mini-events over the phone.

Semantic Memory. Semantic memory was assessed using the Information subtest of the Wechsler Intelligence Scale for Children–5th edition (WISC–V; [15]) for participants ≤16 years or the Wechsler Adult Intelligence Scale–4th edition (WAIS-IV; [16]) for participants ≥16 years, together with a computer-based naming test in which participants had to name 60 pictures. The standardized norms for the Information subtest and the numbers of correct responses for the naming test are reported.

Working Memory. Visuospatial working memory was assessed with the Spatial span subtest (Wechsler blocks) of the Wechsler Nonverbal Scale of Ability for children aged <16 years or the MEM-III for participants aged ≥16 years [17]. Auditory-verbal working memory was assessed with the Digit span subtest of the WISC-V or WAIS-IV, depending on the participant's age. Total normative scores are reported.

Procedural Memory. Perceptuomotor sequence learning was assessed with the Serial Reaction Time Task (SRTT), and motor adaptation with a nonconventional direction writing task [18]. Specific learning scores (in ms) and the number of correct trials in the backward condition were collected.

Non Memory Cognitive Assessment

Global cognitive outcome was assessed with the WISC-V (<16 years [15]) or WAIS-IV (≥16 years [16]). Regarding specific cognitive domains liable to modulate memory processes and recall, language was assessed with the French version of the Peabody Picture Vocabulary Test [19], executive functions with the Trail Making Test (TMT A and B; mental flexibility) and Stroop test ([20,21]; inhibition), attention with the computerized Test of Attentional Performance ([13]; divided attention) and D2 test ([22]; sustained and selective attention), and fine motor skills with the Purdue Pegboard Test.

Irradiation Doses

For irradiated patients, radiation doses were collected from the initial dosimetry plan when available. The right and left hippocampus, anterior and posterior cerebellum and striatum were retrospectively and manually delineated by NC on postoperative T1-weighted images registered with the radiotherapy planning CT scan, and checked by an experienced radiation oncologist (AL) in accordance with European guidelines [23]. Mean radiation doses for both structures are reported as well as mean irradiation dose to the supratentorial brain extracted from the initial dosimetry.

Statistical Analysis

All statistics were performed using jamovi (1.6.15.0) software The jamovi Project, 2021[24].

Performances on the different cognitive tests were subjected to analyses of variance (ANOVAs) between groups (irradiated patients, nonirradiated patients, and controls) and Tukey post hoc tests. A p value <0.05 was considered significant. Bonferroni correction was applied for multiple comparisons. We calculated effect sizes between groups using ω^2: effect sizes between 0.01 and 0.06 were

considered small, those between 0.06 and 0.14 medium, and those above 0.14 large.

Impairment was defined as being within the lowest 5% of scores for a standard population. This corresponded to a percentile rank below 5, a standard score below 5, or a *z* score below -1.65 *SD*s. As memory is a cognitive function that develops during childhood and adolescence, it is important to take age into account. For tests that did not have normative scores for age, we calculated a *z* score from controls using the formula $z = (x - \mu_{age})/\sigma$, where x is the raw score and σ is the *SD* for the control group. As age-dependent data distribution was linear in our control group, we used a linear regression model to determine the age-corrected mean score $\mu_{age} = \alpha + \beta X$, where X is age, α the estimated intercept, and β the estimated slope. SD for the control group was calculated after age correcting mean scores.

After transforming all the data into *z* scores, we used *k*-means cluster analysis to establish participants' memory profiles. Exploratory cluster analyses were performed on reduced and centered variables. The distribution of these profiles was then compared between groups.

Spearman correlations were calculated between mean radiation doses to the left and right hippocampus and declarative memory scores, and between mean radiation doses to the left and right anterior and posterior cerebellum and working memory.

Results

Participants

The sample comprised 60 participants: 22 in the irradiated group, 17 in the nonirradiated group, and 21 in the control group. Patients in the irradiated group were mainly treated for medulloblastomas, with a combination of surgery, chemotherapy, and craniospinal irradiation ($n = 17$). Four of them had ependymomas, and one an atypical teratoid rhabdoid tumor that were treated with surgery and focal radiotherapy. All but one of the patients in nonirradiated group had pilocytic astrocytomas treated with surgery only ($n = 16$). The remaining patient had a medulloblastoma in the first year of life that was treated with surgery and chemotherapy. Participants' characteristics are summarized in Table 1. Patient groups had significantly lower maternal education levels than the control group.

Memory Outcomes

Patients in both the irradiated and nonirradiated groups had lower scores than controls for all the memory systems, and these differences were significant for irradiated patients for working, episodic and semantic memory. Nonirradiated patients had significantly lower working memory scores than controls, but partially spared performances on

Table 1
Participants' characteristics

	Irradiated PFT ($n = 22$)	Nonirradiated PFT ($n = 17$)	Controls ($n = 21$)	*p* value
Demographic characteristics				
Sex (male/female)	17/5[b]	6/11	16/5	0.011
Mean age in years (SD)	17.9 (5.13)	16.4 (5.09)	18.2 (5.22)	0.524
Mean time since end of treatment in years (SD)	8.95 (3.12)	8.94 (2.73)		0.991
Mean maternal education level in years (SD) [range]	12.8 (2.17) [2–8][a]	13.5 (3.36) [3–8]	15.3 (2.55) [2–9]	0.006
Tumor diagnosis and treatment				
Mean age at diagnosis in years (SD) [range]	8.73 (4.26) [1–17]	6.06 (3.82) [0–13]		0.050
Tumor type	1 ATRT 4 EP 17 MB	16 PA 1 MB		
Tumor location				
- Median	17	5		
- Right cerebellar hemisphere	1	8		
- Left cerebellar hemisphere	0	4		
- Missing data	1	0		
Postoperative cerebellar mutism syndrome	4	3		
Hydrocephalus at diagnosis				0.923
- No hydrocephalus (%)	2 (9%)	2 (12%)		
- Hydrocephalus with no treatment (%)	2 (9%)	1 (6%)		
- Hydrocephalus requiring CSF diversion (%)	18 (82%)	14 (82%)		
Chemotherapy	19[b]	1		<0.001
Radiotherapy	5 focal 17 CSI			

Note. ATRT: atypical teratoid rhabdoid tumor; CSI: craniospinal irradiation; EP: ependymoma; MB: medulloblastoma; PA: pilocytic astrocytoma; PFT: posterior fossa tumor; CSF: cerebrospinal fluid.

[a] Significant difference from control group ($p = 0.05$).

[b] Significant difference from PFT group ($p = 0.05$).

episodic and semantic memory. Compared with nonirradiated patients, irradiated patients had significantly poorer working memory and episodic memory performances, especially on word list learning (CMS) and Epireal recall. Their performances did not differ significantly on either visuospatial anterograde memory (face recognition), autobiographical memory, or semantic memory. Although one-way ANOVAs did not highlight significant impairment in procedural memory. Details of memory scores and neuropsychological tests for patients and controls are reported in Table 2.

Memory Impairment According to Group and Test

Results revealed that 86% of irradiated patients and 65% of nonirradiated patients had a deficit in at least one memory system (Figure 1). The percentages of impairment on each test for the nonirradiated and irradiated groups are reported in Figure 2. Half the patients in the irradiated group and a quarter of patients in the nonirradiated one had impaired visual working memory, making this memory system the most impaired in both groups. Concerning episodic memory, the percentage of irradiated patients who performed below the threshold of -1.65 *SD*s on word list learning was very low (<20%), compared with the other tests (around 30%), suggesting that this was not the most efficient test for detecting episodic memory impairment. By contrast, there was a high percentage of impairment on face recognition for the control group (10%), suggesting that this test tends to underestimate performances. For the autobiographical questionnaire and Epireal, both non-standardized tests, impairment was calculated from the control group's *z* scores. The high percentage of impairment in both patient groups on autobiographical memory could be due to the fact that our control group had particularly good verbal skills and a high education level, resulting in particularly high performances on this questionnaire. Finally, a greater difference between nonirradiated and irradiated participants on Epireal suggests that this is a more efficient test for detecting irradiation-induced episodic memory impairment. All nonirradiated patients performed within the normal range on the sum of free recall, cued recall and recognition.

Memory Profiles

K-means analysis across groups and the battery of memory tests revealed three distinct memory clusters

Table 2
Memory scores, standard neuropsychological tests in irradiated patients [G1], nonirradiated patients [G2] and controls [G3]

Tests	Irradiated PFT [G1]	Nonirradiated PFT [G2]	Controls [G3]	*p* value	Post hoc			Effect size (ω^2)
	($n = 22$)	($n = 17$)	($n = 21$)		G1/G2	G1/G3	G2/G3	
Working memory								
Weschler Block - total score (rp)	35.1 (34.9)	54.6 (31.2)	70.9 (24.7)	**0.001**		***		0.18
Digit span - total score (ns)	7.6 (3.0)	9.8 (2.9)	13.3 (2.5)	**<0.001**	*	***	***	0.42
Episodic memory								
Face recognition - delayed (ns)	7.4 (3.6)	8.8 (3.1)	11.0 (3.2)	**0.004**		**		0.15
Word list - learning (ns)	8.7 (3.4)	11.7 (3.4)	13.7 (2.8)	**<0.001**	*	***		0.29
Word list - delayed recall (ns)	9.8 (3.4)	11.4 (3.4)	13.8 (2.2)	**<0.001**		***	*	0.21
AQ - dinner total score	14.4 (3.0)	14.9 (2.1)	15.9 (1.7)	0.119				
AQ - holiday total score	15.6 (2.4)	15.7 (1.6)	17.2 (1.8)	**0.019**		*		0.10
Epireal - free recall	6.0 (3.7)	8.5 (4.1)	10.5 (3.9)	**0.001**		***		0.18
Epireal - total recall	33.6 (2.2)	35.7 (1.0)	35.4 (1.6)	**<0.001**	***	**		0.21
Semantic memory								
Naming - total score	54.4 (3.8)	56.2 (2.3)	58.1 (1.5)	**<0.001**		***		0.23
Information - total score (ns)	8.0 (2.8)	9.4 (3.3)	13.4 (2.3)	**<0.001**		***	***	0.40
Procedural memory								
SRTT- specific sequence-learning score	35.0 (71.2)	39.5 (67.2)	48.0 (33.3)	0.767				
Trigam - correct trial	19.2 (6.5)	21.5 (3.0)	22.6 (2.8)	0.053				
Nonmemory cognitive assessment								
TMT B − A speed score (*z* score)	-2.6 (3.4)	-0.0 (0.8)	0.7 (0.5)	**<0.001**	***	***		0.31
Stroop test − interference score (*z* score)	-1.2 (1.1)	-0.6 (0.8)	0.5 (1.0)	**<0.001**		***	**	0.34
D2 - GZ-F (rp)	25.7 (24)	38 (35.2)	73.9 (25.4)	**<0.001**		***	***	0.35
TAP 2.3 - divided attention - Omissions (rp)	16 (15.9)	36.7 (32.8)	41.0 (26.9)	**0.005**	*	**		0.14
Peabody - total score (rp)	65.5 (32.8)	75.8 (22.0)	94.5 (4.2)	**<0.001**		***	*	0.20
PPT - sum of 3 trials	87.6 (26.8)	108.1 (14.4)	114.2 (20.4)	**<0.001**	*	***		0.21
PPT - assembly	74.8 (26.1)	86.5 (21.5)	114.5 (18.3)	**<0.001**		***	***	0.36

Test results are given as the mean (standard deviation). *Note*. AQ: autobiographical questionnaire; Peabody: Peabody Picture Vocabulary Test; ns: normative score; PFT: posterior fossa tumor; PFT+RT: irradiated posterior fossa tumor; PPT: Purdue Pegboard Test; rp: rank percentile; *SD*: standard deviation; SRTT: Serial Reaction Time Task; TAP: Test of Attentional Performance; TMT: Trail Making Test. * $p < .05$. ** $p < .01$. *** $p < .001$.

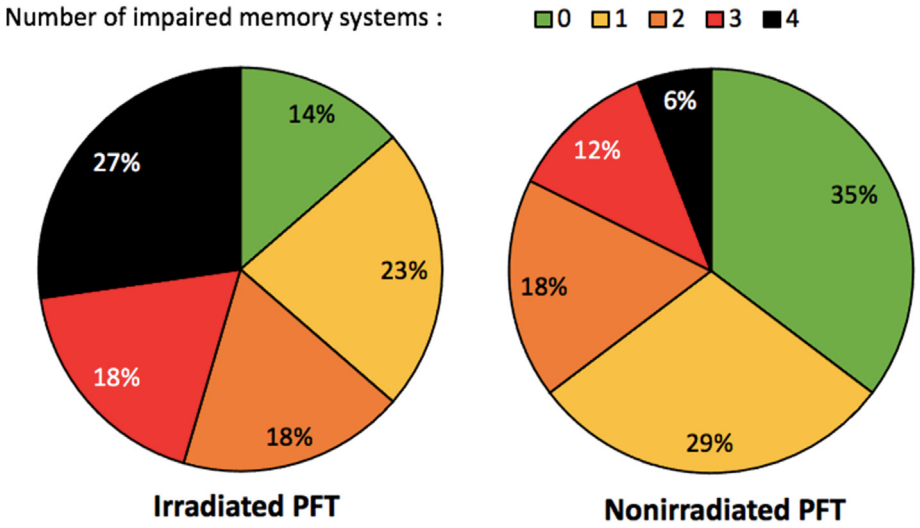

Fig 1. Memory system impairment in irradiated and nonirradiated PFT survivors. Impairment of a memory system was defined as performance < -1.65 *SDs* on at least one test.

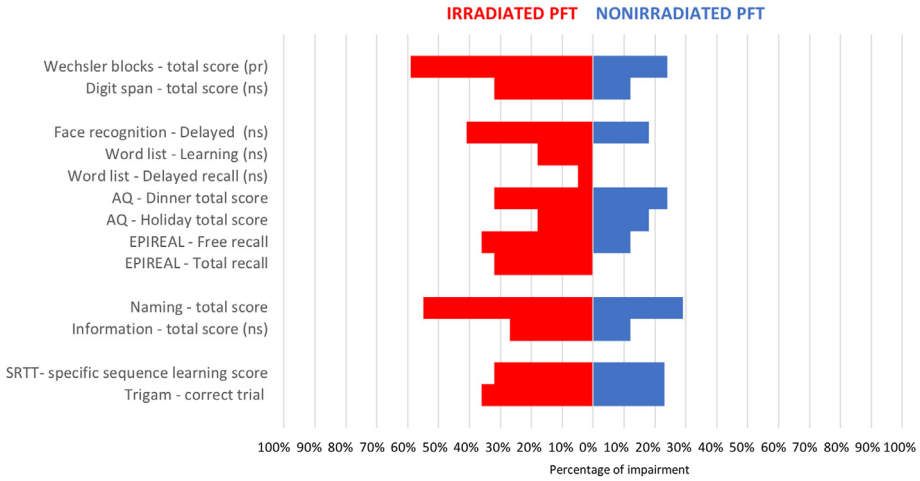

Fig 2. Memory impairment according to test and group. Figure 2 shows percentages of impairment on each test for the nonirradiated (on the right) and irradiated groups (on the left). pr: percentile rank; ns: normative score; AQ: autobiographical questionnaire; SRTT: Serial Reaction Time Task. Impairment was defined as performance < −1.65 *SDs*, using either norms from the standardized tests or the control group's age-corrected *z* scores for the nonstandardized tests.

(Figure 3A). In Cluster 1, performances on all memory tests were within a normal range, between 0 and +2 *SDs*. In Cluster 2, all memory performances were within a normal range between −1 and 0 *SD*, except for visual working memory and naming scores, which were between −2 and −1 *SDs*. In Cluster 3, all performances were within a pathological range below −1.65 *SDs*, except for verbal working memory (between −1.1 and −2 *SDs*), verbal anterograde memory (between −0.5 and −1.3 *SDs*), and the Wechsler Information subtest (−1.3 *SDs*). The distribution of clusters differed significantly between groups, $F(57) = 4.28$, $p = 0.019$, with the main differences being between patient and control groups (irradiated PFT vs. control: $p_{Tukey} < 0.001$; nonirradiated PFT vs. control: $p_{Tukey} = 0.002$) (Figure 3B).

Epireal Test of Episodic Memory

Eight participants (four in irradiated group, three in nonirradiated group, and one in control group) performed the recall over the phone. An analysis of covariance with Epireal scores, phone or in person recall modality, and group as fixed factors, and age as a covariate, revealed nonsignificant effects of phone recall on free recall, $F(53) = 1.29$, $p = 0.260$, episodicity, $F(53) = 0.0279$,$p = 0.870$, and contextual information: what, $F(53) = 1.355$, $p = 0.250$; where, $F(53) = 0.693$,$p = 0.409$; and when, $F(53) = 0.328$, $p = 0.328$. By contrast, there were significant effects on cued recall, with lower scores for phone versus in person recall, $F(53) = 4.064$,$p = 0.049$, and recognition, with higher scores for phone versus in person recall, $F(53) = 20.66$, $p < 0.001$.

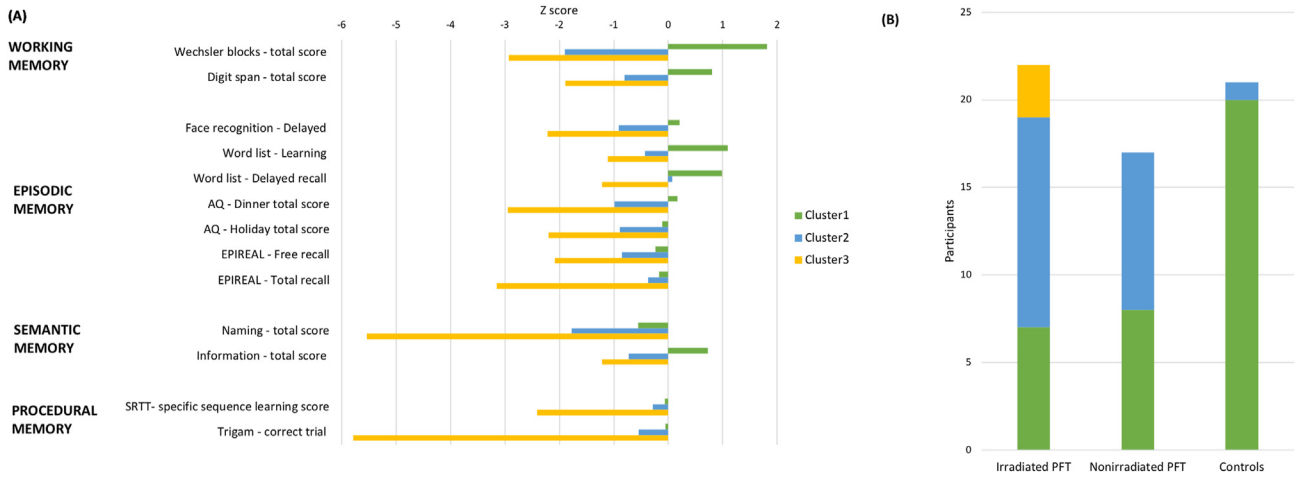

Fig 3. Memory performance profiles. (**A**) Mean z scores for three clusters. (**B**) Distribution of clusters in patient and control groups. AQ: autobiographical questionnaire; SRTT: Serial Reaction Time Task.

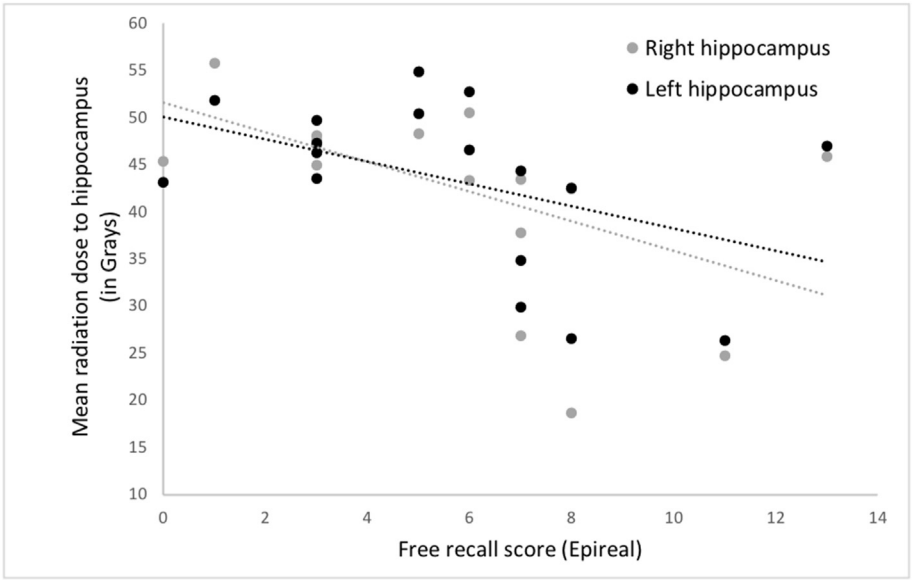

Fig 4. Correlation between mean radiation dose to hippocampus and episodic memory performance.

There was no interaction between group and recall modality.

Impact of Hippocampal Irradiation on Memory Systems

The mean radiation dose to the left hippocampus was 43.40 Gy (*SD*: 8.87, range: 26.36–54.87), and the mean dose to the right hippocampus was 42.70 Gy (*SD*: 10.23, range: 18.73–55.79). A higher dose of radiation to the left hippocampus significantly correlated with lower scores on visual anterograde memory, Epireal free recall, and the autobiographical questionnaire, but not on verbal anterograde memory (Table 3). All patients who scored below 6.5 (−1 *SD* of mean control performance) on free recall in the adapted Epireal test had received more than 40 Gy to the hippocampus (Figure 4). Mean radiation doses to the left and right anterior and posterior cerebellum were similar (52 Gy, *SD*: 6, range: 44–68 for posterior cerebellum, and 55 Gy, *SD*: 6, range: 39–69 for anterior cerebellum). No correlations were found with working memory or procedural memory scores. Mean irradiation doses to the striatum were reported in a previous publication and were not correlated with procedural memory scores too. Mean irradiation to supratentorial brain was 30.39 Gy (SD:12.08, range: 5.95–43.69). Higher dose of supratentorial brain irradiation were correlated with lower score in semantic memory (Spearman's rho:-0.461, $p = 0.047$), anterograde verbal memory (Spearman's rho:-0.465, $p = 0.045$), anterograde visual memory (Spearman's rho:-0.510, $p = 0.026$) and free recall of EPIREAL (Spearman's rho:-0.495, $p = 0.031$).

Discussion

In the present study, we found a high prevalence of memory deficits in pediatric PFT survivors, with at least one

Table 3
Impact of mean hippocampal irradiation dose on declarative memory

		Left hippocampus		Right hippocampus	
		Spearman's rho	*p* value	Spearman's rho	*p* value
Anterograde visual memory	Face recognition - delayed (sn)	−0.496	**0.043***	−0.351	0.168
Anterograde verbal memory	Word list - learning (sn)	−0.298	0.245	−0.274	0.288
	Word list - delayed recall (sn)	−0.174	0.503	−0.158	0.544
Episodic memory	Epireal - free recall	−0.630	**0.007****	−0.477	0.053
	Epireal - total recall	−0.080	0.759	0.036	0.891
Autobiographical memory	AQ - dinner total score	-0.581	**0.014***	−0.578	**0.015***
	AQ - Holiday total score	−0.682	**0.003****	−0.563	**0.019***
Semantic memory	Information - total score (sn)	−0.229	0.376	−0.272	0.290
	Naming - total score	−0.442	0.076	−0.326	0.202

Note. AQ: autobiographical questionnaire; sn = standardized norm. * $p < .05$. ** $p < .01$. *** $p < .001$.

impaired memory system in 86% of irradiated survivors and 65% of nonirradiated survivors. A working memory deficit was a common feature of pediatric PFT cognitive outcome, whereas episodic memory impairment was more specific to the irradiated PFT memory profile.

In line with *cerebellar cognitive affective syndrome* [25], cerebellar damage induced by the tumor, the surgery and, in the irradiated group, by the radiation, affected not only working memory, but also executive functions, including inhibition, attention, and language.

Episodic memory, which is subtended by the mediotemporal lobe, a brain region sensitive to radiotherapy, was preserved in nonirradiated patients and impaired in irradiated patients, with an effect of mean dose to the supratentorial brain and especially to the left hippocampus. Notably, correlation between scores in episodic memory and irradiation dose to the left hippocampus were stronger than with mean supratentorial irradiation dose in line with a specific impact of irradiation on this brain area. Dose to the left hippocampus has already been found to be correlated with WMS-III Word list immediate recall [26] among adult patients with central nervous system metastasis of lung cancer, and with visual and verbal memory in pediatric brain tumor survivors 3 years on average after the end of treatment [6].

In the present study, we found that a commonly used word list learning and recall test underestimated episodic impairment in irradiated PFT survivors. Moreover, the autobiographical questionnaire failed to differentiate between nonirradiated and irradiated patients, suggesting that confounding factors such as language skills impact performances on this tool. Finally, we showed that an ecological test (i.e., Epireal) that controls the encoding of mini-events and tests long-term recall at 3 weeks can feasibly be administered to a pediatric population of PFT survivors. Furthermore, over-the-phone recall could make the test less time-consuming, by avoiding the need to attend a second session. Free recall on this test, scored using a structured rating grid, was significantly impaired in the irradiated PFT group, and correlated with the irradiation dose to the left hippocampus, suggesting that Epireal is more sensitive to radiotherapy-induced damage to the hippocampus. Taken together, these findings suggest that Epireal could prove useful for establishing hippocampal radiotherapy dose constraints.

Concerning procedural memory, deeper statistical analyses have previously revealed motor adaptation impairment in both irradiated and nonirradiated patients, albeit with lower scores for the former [18].

Although this prospective study provided new insights into the long-term impact of a PFT in childhood, it had several limitations. First, the sample was heterogeneous, as it included participants aged 7–26 years, with time since diagnosis ranging from 5 to 15 years, and a variety of tumor types and treatments, reflecting changes in irradiation techniques and prescribed radiotherapy doses over the past 20 years. Medulloblastomas and pilocytic astrocytomas have both a high prevalence among PFT and high 5-year survival rate that make them to be largely represented in studies exploring PFT long-term outcomes. Therefore, our results are particularly generalizable to patients with these tumor types. Concerning ependymomas, their lower prevalence makes a group analysis difficult, but the use of a focal irradiation, limiting the doses to the hippocampus, could lead to a lesser impact on episodic memory. Larger studies are needed to explore this aspect. Second, the impact of chemotherapy on memory could not be addressed in this study, as 19 of the 22 irradiated patients also underwent chemotherapy, compared with just one of the nonirradiated patients. Third, the absence of normative pediatric data for the two novel episodic memory tests (autobiographical questionnaire and Epireal), together with the high cognitive level of our control group limited the interpretation of the impaired memory scores.

Conclusion

Memory impairments are frequent in pediatric PFT survivors. The use of new ecological tests to assess episodic memory is entirely feasible: these tests may be more sensitive to radiation-induced memory impairment than conventional ones, and may also provide more specific markers of the toxicity of medial temporal lobe irradiation and better reflect long-term memory decline.

Ethics statement

The study (NCT04324450) was approved by the national ethics committee (Comité de Protection des Personnes) on 14/10/2019.

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Author contribution

1 guarantor of integrity of the entire study: AL.
2 study concepts and design: AL, JP, YC.
3 literature research: EB, LP.
4 clinical studies: EB, LP, MCa, MCo, NC, BAI.
5 experimental studies/data analysis: EB, LP, NC, MCa, FT.
6 statistical analysis: EB, LP, BL, FT.
7 manuscript preparation: all authors.
8 manuscript editing: all authors.

Conflict of Interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Anne LAPRIE reports financial support was provided by National Cancer Institute.

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